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10/807,096	03/22/2004	Allan Svendsen	10321.200-US	2911
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NOVOZYMES NORTH AMERICA, INC.			MOORE, WILLIAM W	
500 FIFTH AVENUE			ART UNIT	
SUITE 1600			PAPER NUMBER	
NEW YORK, NY 10110			1656	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/807,096

Applicant(s)

SVENDSEN ET AL.

Examiner

William W. Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 22 October 2004.
- 2a) ☐ This action is **FINAL**.
- 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 40-59 is/are pending in the application.
- 4a) Of the above claim(s) 40-55 and 58 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 56, 57 and 59 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 20041027.

- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date: \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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## DETAILED ACTION

*Rescission of Previous Communication*

The requirement for restriction in the communication mailed 12 October 2006, as well as the one month shortened statutory period for response stated therein, are hereby RESCINDED. The requirement for restriction is restated below, together with the commemoration of the election made telephonically by Applicant's counsel on 7 September 2005, and an action on the merits based on the election follows. This communication has a three-month shortened statutory period for response from the date of its mailing and extensions of time may be available under the provisions of 37 CFR 1.136(a) up to a period of six months from the mailing date.

*Priority*

Applicant's claims in the Declaration of Inventorship and in the first page of the specification filed 22 March 2004 to priority under 35 U.S.C. § 119 of the 21 March 2003 filing date of the Danish patent application No. 2003 00435, and to the 26 March 2003 filing date of the US provisional application No. 60/457,798, are hereby acknowledged.

*Information Disclosure Statement*

Applicant's Information Disclosure Statement [IDS] filed on 27 October 2004 is hereby acknowledged.

*Preliminary Amendment*

Applicant's Preliminary Amendment filed with the application on 22 March 2004 has been entered, canceling claims 1-39 and presenting the new claims 40-59, which are subject to the following requirement for restriction.

*Restriction*

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

1. Claims 40-55, each drawn in part to several species of methods for modeling subtilase tertiary structure using the tertiary structure of the subtilase JP170 as a

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reference sequence and altering a subtilase-encoding nucleic acid sequence to provide a modified primary sequence having a different, generic, property, classified in class 435, subclass 471.

2. Claims 56-59, each drawn in part to several species of modified subtilases having at least one amino acid sequence modification within 10Å of an ion-binding site in a JP170-like subtilase at positions numbered by correspondence with the 433-amino acid sequence of SEQ ID NO:1, classified in class 435, subclass 219.

Inventions of Groups 1 and 2 are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the species of molecular modeling methods of Group 1 require modification(s) of a polynucleotide and the use thereof in recombinant expression of a variant product but the diverse species of variant products of Group 2 can be made by a materially different process, such as solid-phase chemical synthesis.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

- A. Claims 40-44 of Group 1 are generic to the following disclosed patentably distinct species of methods:

- a) at least seven methods of identifying (an) amino acid sequence modification(s) in any of seven beta-sheet strands of a JP170 subtilase,
- b) at least six methods of identifying (an) amino acid sequence modification(s) in any of six alpha helices of a JP170 subtilase,
- c) at least three methods of identifying (an) amino acid sequence modification(s) altering the position(s) of an aspartate c-alpha atom in one or all of three ion binding sites of a JP170 subtilase,
- d) at least three methods of identifying (an) amino acid sequence modification(s) altering the position(s) of a histidine c-alpha atom in one or all of three ion binding sites of a JP170 subtilase,
- e) at least three methods of identifying (an) amino acid sequence modification(s) altering the position(s) of a serine c-alpha atom in one or all of three ion binding sites of a JP170 subtilase, and

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f) at least three methods of identifying (an) amino acid sequence modification(s) altering the position(s) of a next-to-serine c-alpha atom in one or all of three ion binding sites of a JP170 subtilase.

B. Claims 40 and 45-55 of Group 1 are generic to the following disclosed patentably distinct species of methods:

a) at least three methods of identifying (an) amino acid sequence modification(s) that remove(s) one or more of three ion binding sites from a JP170 subtilase,

b) at least one method of identifying (an) amino acid sequence modification(s) that alter(s) the mobility of a mobile region of a JP170 subtilase,

c) at least one method of identifying (an) amino acid sequence modification(s) that introduce(s) a disulfide bond by insertion of, or substitution with, at least one cysteine in a JP170 subtilase,

d) at least one method of identifying (an) amino acid sequence modification(s) that alters the charge distribution of amino acids on the surface of a JP170 subtilase by replacing an uncharged amino acid with a charged amino acid,

e) at least one method of identifying (an) amino acid sequence modification(s) that alters the charge distribution of amino acids on the surface of a JP170 subtilase by replacing a charged amino acid with a differently-charged amino acid, and

f) at least one method of identifying (an) amino acid sequence modification(s) that improves the thermal stability of a JP170 subtilase by identifying (a) position(s) for the substitution of a native amino acid by a proline, and

g) at least three methods of identifying (an) amino acid that resides at a position within a distance of 10A from any of the three active site residues of a JP170 subtilase.

C. Claims 56-59 of Group 2 are generic to at least one hundred and fifty species of modified JP170 subtilase as determined by the more than one hundred and fifty amino acid positions recited as sites for modification in claims 57, 58 and 59..

The species are independent or distinct because no species of method of identification of the claims of Group 1 requires the application of, or is contingent upon, another species of method of identification and because no species of modified product of the claims of Group 2 requires the modification of, or is contingent upon modification of, at another amino acid position where the recitations of claims 57 and 58 avoid any requirement in reciting "preferably", and "optionally". Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is

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traversed. Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

#### *Election*

During a telephone conversation with Mr. Elias J. Lambiris on 7 September 2005 a provisional election was made with traverse to prosecute the invention of Group 2, claims 56-59. A further provisional election was made with traverse of the species of JP170-like subtilase modified by an amino acid substitution at a position corresponding to S193 in SEQ ID NO:1 herein. Affirmation of this election must be made by applicant in replying to this Office action. Claims 40-55 and 58 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as drawn to a non-elected invention where claim 58 excludes the elected species and, because the elected species of modification at a position corresponding to S193 in SEQ ID NO:1 herein was found to be free of the prior art, further species of claims 56, 57, and 59 are examined herein.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR §1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR §1.48(b) and by the fee required under 37 CFR §1.17(h).

#### *Objection to the Specification*

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This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). In particular, Figures 1 and 4 contain amino/nucleic acid sequences, which are not identified by a sequence identification number. Also, Tables of atomic coordinates, e.g., at pages 74-302 of the specification, represent the disclosure of linear amino acid sequence and therefore are required to have a heading indicating a sequence identification number. Applicant's attention is directed to 37 CFR 1.821, which states:

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, each time that reference is made to the JP170 subtilase in the specification, or to the amino acid sequence of another, specific, subtilase e.g., at pages 3-5, 8-11, 15, 18-20 (with respect to positions enumerated), and 22, or in the claims, it should be accompanied by the sequence identifier, e.g., "SEQ ID NO:1". Compliance is required in response to this communication.

#### *Claim Objections*

Claim 57 is objected to because of the following informalities: The transition between the claim's preamble and each of the clauses (a) - (c) is misleading and clauses (b) and (c) are in part redundant in naming common positions for modification. Appropriate correction is required.

#### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. § 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

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connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56, 57 and 59 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of the "variant JP170 type subtilases" of claims 56, 57, and 59 where a variant that comprises an amino acid substitution at a position recited in the claims may itself be a "variant" subtilase unrelated to any particular "JP170 type" subtilase. Claims 56 and 59, however, recite **"variant comprising** at least one modification in a position", expressly embracing modifications at any number of amino acid positions beyond the positions recited in the claims because the modified molecule need have no particular relationship to the amino acid sequence set forth in SEQ ID NO:1, the disclosed amino acid sequence of the mature JP170 subtilase. Claims 56, 57 and 59 therefore permit modifications at other, non-specified, positions, beyond the 151 positions recited in these claims because they require no definite degree of structural relationship between the amino acid sequence of SEQ ID NO:1 and that of a "variant", "JP170 type", subtilase. The specification fails to describe either where the further, unrecited, positions occur or what the differences might be, and does not otherwise disclose or suggest the nature or source of any of the generic proteins that meet the broad claim limitations. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics of "variant" subtilases that diverge at unspecified and numerous amino acid positions from the sequence set forth in SEQ ID NO:1, nor does it provide characteristics permitting a correlation between the undisclosed structures of "variant" subtilases



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among the myriad members of the genus of claims 56-59 and a variant wherein the amino acid sequence of SEQ ID NO:1 is modified at one or more of the positions specifically recited in claims 56-59.

Claims 56, 57, and 59 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation of a variant JP170 subtilase wherein the variant subtilase has an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO:1 due to an amino acid sequence modification at one or more of the 151 positions recited in claims 57-59, does not reasonably provide enablement for the preparation and use of a variant subtilase having 23 or more amino acid sequence modifications in the amino acid sequence set forth in SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 56, 57, and 59 contemplate, as noted at page 3 above, numerous, arbitrary, amino acid substitutions, additions, or deletions in generic proteins that differ to an unspecified extent from the primary structure represented in the sequence of SEQ ID NO:1, the disclosed amino acid sequence of the mature JP170 subtilase. Specific substituent amino acids are indicated for only 14 of the 151 amino acid positions within SEQ ID NO:1 recited in claims 57-59 and the elected claims do not require that the unspecified substituents, or additions or deletions of amino acids, at any of the other 139 positions have a particular result on even the disclosed JP170 subtilase of SEQ ID NO:1 after modification. At most, the elected claims require only that the resulting modified, molecule function as a subtilase, i.e., has serine protease activity, but mere sequence perturbation cannot enable the design and preparation of divergent subtilases and provide the public with subtilases that retain proteolytic activity. This rejection is stated under the first paragraph of the statute because the specification cannot support introduction of an unspecified number of amino acid modifications in the amino acid sequence of SEQ ID NO:1, even if the greatest number is limited to the 151 positions recited in the claims, where amino acid insertions, deletions, or substitutions, in any combination or any pattern, provide a functioning protease. Indeed, the specification

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cannot identify amino acids that might be suitable substituents for 139 of the positions recited in the claims that support the retention of catalytic activity of the resulting variant.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. § 112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing eight factors relevant to analysis of enablement). Applying the

factors discussed in *Wands* to Applicant's disclosure, it is apparent that:

- a) the specification lacks adequate, specific, guidance for altering the amino acid sequence of the reference JP170 subtilase having the amino acid sequence of SEQ ID NO:1 to the extent permitted in claims 56, 57 and 59,
- b) the specification lacks working examples wherein the amino acid sequence of the reference JP170 subtilase having the amino acid sequence of SEQ ID NO:1, is altered to the extent permitted in claims 56, 57 and 59,
- c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
- d) unpredictability exists in the art where no members of the class of mature subtilases having amino acid sequences of about 344 amino acids represented by the reference amino acid sequence of SEQ ID NO:1, have had even a few amino acid positions identified for concurrent modification.

Thus the scope of subject matters embraced by the phrase, "variant comprising at least one modification in a position", is unsupported by the present specification, if combined with teachings available in the prior art, particularly where claims 56, 57 and 59 must be construed to permit modifications at a large number of positions recited in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 56, 57 and 59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 56 and 57 are indefinite because there is no fixed point, or coordinate, provided for measuring the subject matter indicated by the phrase "modification in an

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amino acid residue in a position located at a distance of 10Å (6 Å) or less to". The specification does not define such residues, or the site for measuring the atoms that constitute the residues, in the sphere(s) alternatively indicated in the claims, thus the public and artisan seeking to ascertain the metes and bounds of the claimed subject matter cannot know the number of residues embraced by the claims. Claim 57 is included in this rejection because it depends from claim 56 and recites "in at least one", thereby permitting other, unspecified, residues that might be encompassed, but not identified by, claim 56.

Claims 56, 57 and 59 are indefinite where the terms "preferably", which occurs once in each of claims 56, 57 and 59, render these claims indefinite because it is unclear whether the limitation(s) following these phrases are part of the claimed invention. See MPEP § 2173.05(d). In this national forum, the proper form for presenting multiple, related, subject matters in patent claims is to provide claims of different scope where (an) initial claim(s) describe(s) only the subject matter having the broadest scope now present in each of the rejected claims and is followed by one or more dependent claim(s) that refer(s) back to the initial claim and that describe(s) subject matter(s) of progressively lesser scope that now follow the terms "preferably" and "optionally" in claims 56-58, wherein the terms "preferably" and "optionally" are no longer present. It is noted that in the case of claim 57, it may be desirable to provide a separate claim that recites a subset of the currently-recited positions that are within a distance of 6Å or less of an ion-binding site. Providing such a set of amended and/or new claims will overcome this aspect of the rejection.

Claim 57 is further indefinite because it fails to state definite and distinct subject matter where several positions for modification recited in clause (b) of the claim are also recited in clause (c) of the claim and the claim does not make it clear whether

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modifications are to be in at least one position in the entire molecule, in which case dividing the several positions into separate ion-binding site regions is misleading, or are to be made in at least one position in at least one ion-binding site, in which case the conjunction "and" must follow "393," in line 6 of the claim, or in at least one position in each binding site, in which case "and" must follow "393," in line 6 of the claim and the phrase "in at least one of the positions" must be removed from the preamble of the claim in and inserted before recitations of, e.g., "of the ion-binding site 1" in clause (a) of the claim and similarly inserted in clauses (b) and (c) of the claim. This problem is compounded by the failure to relate the numbers of the positions to any particular amino acid sequence thus the artisan and the public seeking to ascertain the metes and bounds of the intended subject matter cannot distinguish between, e.g., a 183<sup>rd</sup> amino acid numbered from the amino terminus of a precursor, or preprosubtilase, a 183<sup>rd</sup> amino acid numbered from the amino terminus of a prosubtilase, and a 183<sup>rd</sup> amino acid numbered from the amino terminus of a mature subtilase. Too many issues of indefinite description arise to propose corrective, amendatory, language for claim 57.

Claim 59 is indefinite because it fails to state definite and distinct subject matter where it recites, "**comprising** at least modification in a position selected from the group **comprising** positions" (emphases supplied), thus leaving the scope of the claim open to modifications at positions beyond the "group comprising" that are unrecited, thus unknown. The artisan and the public seeking to ascertain the metes and bounds of the intended subject matter cannot distinguish between the further positions intended for modification and the further positions not intended for modification. Amending the claim to recite a proper Markush group, e.g., **comprising** at least modification in a position **selected from the group of positions consisting of positions**" (emphases supplied), will overcome this aspect of the rejection.

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Claims 57 and 59 are indefinite because they fail to state (a) sequence identifier(s) for the amino acid sequence(s) of a subtilase(s) that will permit the recognition of any intended position. While the particular amino acid sequence of the reference, prior art, JP170 subtilase set forth in SEQ ID NO:1, is disclosed in the specification, claims 57 and 59 cannot identify the context in which the designated positions occur in order that an additional amino acid, or lack thereof, occurring elsewhere in a particular protease amino acid sequence create no ambiguity in interpreting the claims. This rejection may be overcome by amending claims 57 and 59 to insert a further clause that states a disclosed sequence identifier, e.g., SEQ ID NO:1, "wherein said positions correspond to the amino acid positions of SEQ ID NO:1".

*Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 59 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Sloma et al., US 5,891,701, in view of Zukowski et al., US 5,397,705, both made of record herewith.

Sloma et al. teach the amino acid sequence of the mature *Bacillus* JP170 subtilase, which is the amino acid sequence set forth in SEQ ID NO:1 herein. See SEQ ID NO:42 of Sloma et al. Although Sloma et al. teach that conservative amino acid substitutions may be made in the amino acid sequence of the JP170 subtilase, they do not teach any particular positions or regions within the amino acid sequence of the JP170 subtilase for the substitution of amino acids. See columns 2 and 3. Although Sloma et al. propose that the JP170 subtilase be crystallized and its three-dimensional structure determined, they do not teach its three-dimensional structure and do not teach the locations of any

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ion binding sites of the JP170 subtilase. See column 5. Sloma et al. teach, however, that amino acid substitutions should be made in the JP170 subtilase for a set of reasons amino acid substitutions have been made in the art in other subtilases, e.g., modifying the thermostability, oxidative stability, specific activity, and pH optimum of the native subtilase. See col. 5 at lines 8-14.

Thus the teachings of Zukowski et al. are combined with the teaching of Sloma et al. where Zukowski et al. go further than teaching certain positions within a calcium ion binding site that may be modified to reinforce calcium binding to produce increased thermal stability of a *Bacillus subtilis* subtilase at columns 7 and 8, to further teach that other amino acid substitutions at positions beyond those that contribute to an ion binding site will also increase stability of the modified subtilase by comparison with the unmodified subtilase. Zukowski et al. specifically teach that any subtilase can be modified to improve its stability by replacing either an asparagine or a glycine within an asparagine-glycine pair with any of isoleucine, serine, valine, cysteine, glutamine, or threonine. See the text beginning at line 37 of column 6 through line 22 of column 7 and claims 1, 2, and 10-16. Zukowski et al. also teach that replacing a methionine in a subtilase amino acid sequence, whether within or outside the active site region, with an alanine or leucine will provide an improved oxidative stability in the modified subtilase. See the text at lines 23-47 of column 7 and claims 1, 2, 6, 7 and 16. It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Zukowski et al. to the teachings of Sloma et al. of the JP170 subtilase amino acid sequence to make a variant of claim 59 by replacing the glycine at positions 67 and/or 376 of the JP170 subtilase, or the asparagine at positions 134 and/or 375 of the JP170 subtilase, because Zukowski et al. teach that abolishing the occurrence of an asparagine-glycine pair any subtilase by making such amino acid modifications will

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provide a subtilase variant with increased stability. It would also have obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Zukowski et al. to the teachings of Sloma et al. of the mature JP170 subtilase amino acid sequence to make a variant of claim 59 by replacing one of more of the methionines at positions 42, 97, and 153 of the mature JP170 subtilase because Zukowski et al. teach that replacing methionines wherever they occur in a subtilase will provide a subtilase variant with increased oxidative stability. Such an artisan would have had a reasonable expectation of success in making such substitutions because Sloma et al. suggest that the mature JP170 subtilase can advantageously be modified according to teachings of the prior art to achieve the purposes taught in the prior art.

#### Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore  
13 October 2006

  
NASHAAT T. NASHED PHD.  
PRIMARY EXAMINER